UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte SHINICHIRO KUROSAWA and
DEBORAH J. STEARNS-KUROSAWA

Appeal No. 2006-1100
Application No. 10/028,741

ON BRIEF[1]

Before SCHEINER, ADAMS, and GRIMES Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-16, which are all the claims pending in the application.

Claim 1 is illustrative of the subject matter on appeal and is reproduced below:

1. A method for monitoring effective thrombin levels in a human patient undergoing anticoagulant therapy comprising measuring circulating levels of soluble endothelial protein C receptor (sEPCR) of said patient, wherein lowered sEPCR levels relate to lowered effective thrombin activity.

[1] Appellants waived their request for oral hearing. Paper received May 1, 2006. Accordingly, we considered this appeal on Brief.

The references relied upon by the examiner are:

Hirsh et al. (Hirsh), "Oral Anticoagulants: Mechanism of Action, Clinical Effectiveness, and Optimal Therapeutic Range," Chest, Vol. 114, No. 5, pp. 445S-469S (1998)

Kurosawa et al. (Kurosawa), "Plasma levels of endothelial cell protein C receptor are elevated in patients with sepsis and systemic lupus erythematosus; lack of correlation with thrombomodulin suggests involvement of different pathological processes," Blood, Vol. 91, pp. 725-26 (1998)

Esmon et al. (Esmon), "Endothelial Protein C Receptor," Thrombosis and Haemostasis, Vol. 82, No. 2, pp. 251-58 (1999)

References discussed but not relied upon by the examiner:

Debeir et al. (Debeir), "Pharmacological characterization of protease-activated receptor (PAR-1) in rat astrocytes," Eur. J. Pharm., Vol. 323, pp. 111-17 (1997)

Giuidici et al. (Giuidici), "Antithrombin replacement in patients with sepsis and septic shock," Haematologica, Vol. 84, pp. 452-60 (1999)

Kahn et al. (Kahn), "Protease-activated receptors 1 and 4 mediate activation of human platelets by thrombin," J. Clin. Invest., Vol. 103, No. 6, pp. 879-87 (1999)

Gu et al. (Gu), "Endotoxin and thrombin elevate rodent endothelial cell protein C receptor mRNA levels and increase receptor shedding in vivo," Blood, Vol. 95, No. 5, pp. 1687-93 (2000)

GROUND OF REJECTION

Claims 1-16 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the combination of Esmon, Kurosawa and Hirsh.

We reverse.

DISCUSSION

The invention of appellants' independent claim 1 is drawn to a method for monitoring effective thrombin levels in a human patient undergoing anticoagulant therapy.[2] The method comprises a single step - measuring circulating levels of soluble endothelial protein C receptor (sEPCR) of said patient. In addition, the claim requires that lowered sEPCR levels relate to lowered effective thrombin activity. The examiner finds (Answer, pages 3-4), appellants' claimed invention is obvious over the combination of Esmon, Kurosawa and Hirsh.

According to Esmon (page 251, column 1, first paragraph, endnote omitted), "[t]he protein C anticoagulant pathway plays a critical role in the negative regulation of the blood clotting response." In addition, Esmon reports that "[i]n addition to controlling thrombotic events, the protein C pathway appears to be important in regulating the host response to inflammation, particularly sepsis." Esmon, page 253, column 1, first paragraph. Esmon notes, however, that the precise role that activated protein C plays in septic shock is unclear. Esmon, page 253, column 2, third full paragraph. In this regard, Esmon points out that "[t]he initial hypothesis was that EPCR might be involved in the anti-inflammatory mechanisms of the protein C pathway." Esmon, page 254, column 2. Therefore, Esmon "examined the influence of [sepsis related] endotoxin on EPCR expression in vivo using a rat model of septic shock." Id.

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[2] Claim 10, the only other independent claim on appeal, is drawn to "[a] method for monitoring effectiveness of anticoagulant therapy in a human patient comprising measuring circulating sEPCR levels of said patient, wherein decreases in sEPCR indicate that the anticoagulant therapy is effective."

As a result of this study, Esmon report that the rat model of septic shock demonstrated that while the level of EPCR in tissue did not increase, "there was a substantial increase [of sEPCR] in the plasma. . . ." Id. In this regard, Esmon state that "[t]hrombin appears to be the major mediator that causes increased [EPCR] shedding. . . ," resulting in the increase of sEPCR in the plasma. Esmon also point out that the thrombin inhibitor hirudin can block increases of circulating EPCR levels in the septic rat model. Esmon, page 254, column 2, last full paragraph through page 255, column 2, first full paragraph. Therefore, Esmon conclude (id.),

> [b]ased on the vascular location of EPCR on large vessels and the apparent thrombin-mediated shedding, it would appear that monitoring plasma EPCR levels might provide an indication of large vessel disease activity associated with thrombin generation. This could prove useful in monitoring the progression of cardiovascular disease or the effectiveness of therapeutic interventions in these patients.

Esmon notes, however, that

> [t]he protein C pathway is exceedingly complex, and many of the mechanisms by which it mediates its critical functions remain poorly understood. It is likely that additional receptors will be identified that participate in this pathway. Understanding their role in the regulation of coagulation and inflammation will contribute to our understanding of the pathogenic mechanisms of thrombotic disease and contribute to the design of safer and more effective treatments.

Esmon, page 256, column 1.

Notwithstanding the foregoing discussion, the examiner finds (Answer, page 3), Esmon teaches "a method of monitoring thrombin levels in patients undergoing anticoagulant therapy. . . ." In our opinion, the examiner has overstepped the teaching of the reference wherein Esmon, at best, speculates

that "monitoring plasma EPCR levels might provide an indication of large vessel disease activity associated with thrombin generation [and that] [t]his could prove useful in monitoring the progression of cardiovascular disease or the effectiveness of therapeutic interventions in these patients." Brief, bridging paragraph, pages 4-5. Cf. Answer, page 3.

We recognize the examiner's finding (id.) that Esmon's method comprises the administration of hirudin (a specific thrombin inhibitor), and measuring circulating[3] levels of endothelial protein C receptor (EPCR). However, while Esmon does teach that hirudin is a specific thrombin inhibitor and can block increases of circulating EPCR levels[4], the examiner fails to direct our attention to, and we are unable to find, any teaching in Esmon of measuring circulating EPCR levels in a patient undergoing anticoagulation therapy. Cf. appellants' claims 1 and 10.

Nevertheless, the examiner finds (Answer, page 3) that Esmon refers[5] to Kurosawa who reports "that soluble EPCR (sEPCR) was present at high levels in the plasma of normal individuals and was increased several fold in patients with diseases associated with hypercoagulation (autoimmune disorders and septic shock, specifically systemic lupus erythematosis. . .)." In this regard, the examiner finds (Answer, page 4), Kurosawa "teach detection of sEPCR by ELISA in human patient blood plasma. . . ." According to the examiner (id.),

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[3] According to the examiner, since the EPCRs are circulating in the blood they are "necessarily soluble." Id.

[4] Esmon, bridging paragraph, pages 254-255.

[5] See Esmon, page 258, column 2, endnote 75.

Kurosawa reports that "[t]ests showed that in patients with diseases often complicated by thrombotic tendency and hypercoagulation, levels of sEPCR were significantly increased compared to normal control humans."

Notwithstanding the examiner's assertions, Kurosawa concludes, "there are no candidates for an endothelium-specific marker that can show large-vessel disease progression." According to Kurosawa (page 726, column 2, last sentence), "[c]linical studies with defined patient groups will be required to establish the utility of soluble plasma EPCR as a marker of large-vessel disease processes." Therefore, like Esmon, Kurosawa provides an invitation to explore the possibility of whether soluble plasma EPCR levels can be used to monitor disease processes.[6]

As for Hirsh, the examiner finds (Answer, page 4), Hirsh "teach[es] oral anticoagulant therapy for human patients with the anticoagulant[s] Warfarin . . ." and heparin . . . ."[7] Cf. appellants' claims 2-4 and 10-12. In addition, the examiner finds, Hirsh teaches "monitoring the effectiveness of anticoagulant therapy by measuring the prothrombin time (PT) as an international normalized ratio [(INR)] . . . [and] points out that monitoring PT alone is not as reliable a measure of effectiveness of antithrombin therapy as the measure of both PT and INR. . . ." Answer, page 4. According to the examiner (id.), "since Hirsh . . . discussed the difficulties in using PT and INR for monitoring anticoagulation therapy effectiveness, one of ordinary skill in the art would have desired to use a

[6] In addition, we find it noteworthy that like Esmon, Kurosawa does not discuss patients undergoing anticoagulation therapy.

more consistent measurement and one that involved testing a single thing (sEPCR) instead of multiple interacting things (PT and INR)."

We disagree. The examiner's assertions notwithstanding, for the foregoing reasons it is our opinion that the combination of Esmon and Kurosawa provides a person of ordinary skill in the art with nothing more than an invitation to explore a promising new field of experimentation – e.g., whether soluble plasma EPCR levels can be used to monitor disease processes. However, as set forth in In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988):

> The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. ... In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

In our opinion, the rejection of record fits the second kind of error set forth by O'Farrell, wherein the evidence relied upon by the examiner suggests, at best, the exploration of a promising field of experimentation.

To establish a prima facie case of obviousness, there must be both some suggestion or motivation to modify the references or combine reference teachings and a reasonable expectation of success. In re Vaeck, 947 F.2d 488,

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[7] The examiner also finds (id.), Hirsh teaches "the use of a vitamin K antagonist in anticoagulant therapy...."

493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). In the absence of a reasonable expectation of success one is left with only an "obvious to try" situation which is not the standard of obviousness under 35 U.S.C. § 103. See O'Farrell, supra.

In our opinion, Hirsh's teaching of the use of warfarin, heparin and vitamin K antagonist fails to make up for the deficiencies in the combination of Esmon and Kurosawa. Similarly, Hirsh's teaching that monitoring PT and an INR is more reliable that monitoring PT alone also fails to make up for the deficiencies in the combination of Esmon and Kurosawa.

On reflection, it is our opinion that the examiner failed to meet her burden[8] of providing the evidence necessary to establish a prima facie case of obviousness. Accordingly, we reverse the rejection of claims 1-16 under 35 U.S.C. § 103(a) as being unpatentable over the combination of Esmon, Kurosawa and Hirsh.

REVERSED

Toni R. Scheiner
Administrative Patent Judge

Donald E. Adams
Administrative Patent Judge

Eric Grimes
Administrative Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

[8] The initial burden of presenting a prima facie case of obviousness rests on the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

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